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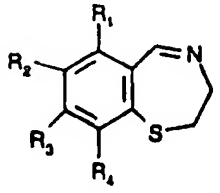
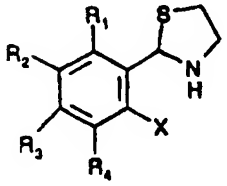


(I)



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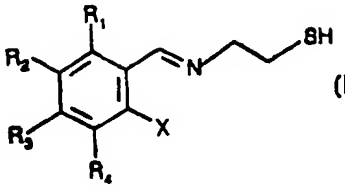

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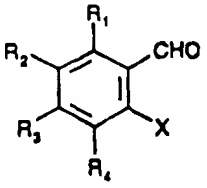

(IV)

$H_2N(CH_2)_2SH$ (V)

(57) Abstract

The application concerns compounds (I) wherein R_1, R_2, R_3 and R_4 are H, halo, (halo)alkyl or (halo)alkoxy, which are prepar from compounds (II) or (III), or directly from compounds (IV) and (V): $H_2N(CH_2)_2SH$ by treatment with a base. Compounds (II) or (II wherein R_1 is chloro, R_2, R_3 and R_4 are H, and X is fluoro, are also claimed. The compounds (I) can be reduced to the correspondi dihydro derivatives, which are useful in the preparation of therapeutical agents.

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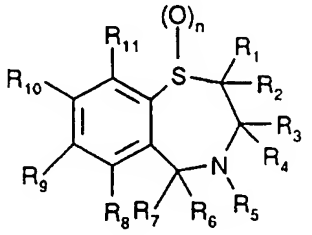
2,3-DIHYDRO-1,4-BENZOTHIAZEPINES, THEIR PREPARATION AND THEIR USE AS INTERMEDIATES

This invention relates to novel 2,3-dihydro-1,4-benzothiazepines, to processes for their preparation and to their use as intermediates in the synthesis of 2,3,4,5-tetrahydro-1,4-benzothiazepines which are useful therapeutic agents.

Compounds of formula A



A

in which:

n = 0, 1 or 2;

R_1, R_2, R_6 and R_7 independently represent H or alkyl of 1 to 4 carbon atoms (optionally substituted with one or more halo);

R_3 and R_4 independently represent H or alkyl of 1 to 4 carbon atoms; or together represent a group of formula $=NR_{12}$ where R_{12} represents H, hydroxy, alkyl of 1 to 4 carbon atoms, phenyl or alkoxy of 1 to 4 carbon atoms; each alkyl, phenyl and alkoxy being optionally substituted with one or more halo;

R_5 represents: (a) H, (b) alkyl of 1 to 4 carbon atoms, (c) a group of formula $-COR_{13}$ in which R_{13} represents H, alkyl of 1 to 4 carbon atoms or phenyl, when R_3 and R_4 represent H or alkyl (optionally substituted with one or more halo), or (d) a group of formula $-S(O)_pR_{14}$ in which p = 1 or 2 and R_{14} is alkyl of 1 to 4 carbon atoms or phenyl, when R_3 and R_4 represent H or alkyl (optionally substituted with one or more halo); each alkyl and phenyl being optionally substituted with one or more halo;

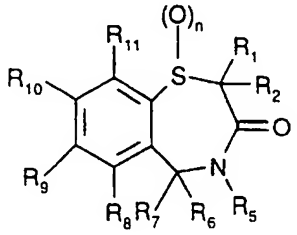
R_8 to R_{11} independently represent H, halo, cyano, nitro, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, alkanoyl of 1 to 4 carbon atoms, carboxy, alkanoyloxy of 1 to 4 carbon atoms, carbamoyl (optionally substituted with alkyl of 1 to 4 carbon atoms) or sulphamoyl (optionally substituted with alkyl of 1 to 4 carbon atoms); each alkyl, alkoxy, alkanoyl and alkanoyloxy being optionally substituted with one or more halo;

their stereoisomers; and

pharmaceutically acceptable salts thereof;

with the provisos that when n = 0; at least one of R_1 to R_{11} is other than H; are disclosed in WO94/11360 as therapeutic agents useful in the treatment of seizures and/or neurological disorders such as epilepsy and/or as neuroprotective agents to protect against conditions such as stroke.

The principal synthetic route to compounds of formula A disclosed in WO94/11360 involves the reduction of compounds of formula B



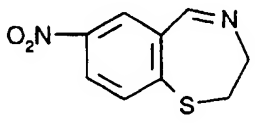
B

using lithium aluminium hydride.

The process suffers from the disadvantage that lithium aluminium hydride is a very powerful reducing agent and reacts vigorously with water. Therefore precautions must be taken to ensure that air and water are excluded from the reaction vessel. Such precautions require the use of sophisticated chemical plants which are expensive to operate. In addition side reactions may occur with lithium aluminium hydride, for example dehalogenation, due to the fact that it is such a powerful reducing agent.

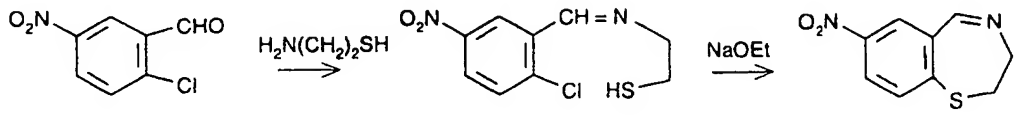
Compounds of formula B are prepared as described in WO92/21668 by reacting 2-mercaptobenzylamine derivatives with ethyl bromoacetate in the presence of base. The preparation of substituted 2-mercaptobenzylamines involves a three step process in which one step involves the use of lithium aluminium hydride. The yields in these steps are poor with the result that the overall yield of compounds of formula A from commercially available starting materials is low.

Compound C



C

is disclosed in Eur.J.Med.Chem. 23 (1988), 403. The compound is prepared by the following sequence:

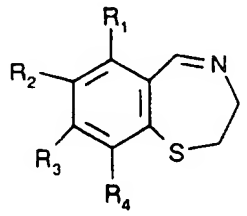


1 2 3

In this sequence the chlorine in 2 is activated towards nucleophilic displacement by sulphur by the presence of the nitro group. Surprisingly it has been found that the presence of the nitro group is unnecessary and that good yields are obtained without this activating group.

A novel process, for the preparation of compounds of formula A, has been found which reduces the number of synthetic steps and improves the overall yield of product. The process involves the use of novel intermediate compounds.

The present invention provides a process for the preparation of compounds of formula I

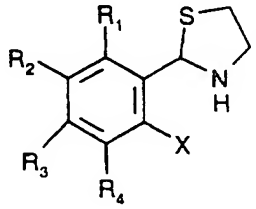


I

in which

R_1, R_2, R_3 and R_4 independently represent H, halo, alkyl of 1 to 4 carbon atoms or alkoxy of 1 to 4 carbon atoms each alkyl and alkoxy being optionally substituted with one or more halo;

comprising ring opening and re-cyclising a compound of formula II



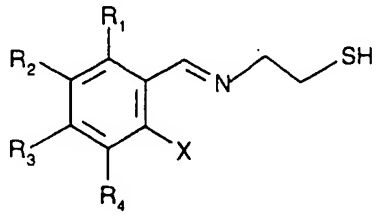
II

in which

R_1, R_2, R_3 and R_4 are as previously defined and X is a group which is susceptible to nucleophilic displacement by sulphur;

in the presence of a base in the presence of an inert diluent.

The compounds of formula II are in equilibrium with compounds of formula III



III

wherein R_1, R_2, R_3 and R_4 are as defined previously. Hereinafter, the compounds of formulae II and III are referred to as being tautomers of each other

It will be understood by those skilled in the art that compounds of formula III or a salt thereof or any combination of II and III may be used in the process. It is believed that compounds of formula II and III are novel and they are claimed as a further aspect of the present invention. A preferred compound of formula II is 2-(2-chloro-6-fluorophenyl)thiazolidine. A preferred compound of formula III is N-(2-chloro-6-fluorobenzylidene)-2-mercaptoethylamine.

Suitably X is chloro, bromo, fluoro, iodo or nitro. Preferably X is fluoro or chloro. More preferably X is fluoro.

It will be appreciated by those skilled in the art that if R_1 represents halo then competing side reactions may occur if there is unsymmetrical substitution in the phenyl ring. Preferably X is chosen so that it is more susceptible to nucleophilic displacement than R_1, for example X is fluoro and R_1 is chloro.

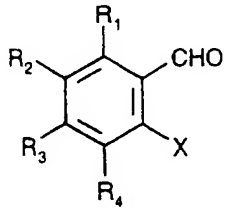
Suitably the base is selected from the group consisting of alkali metal hydroxides, alkali metal hydrides, alkali metal alkoxides or metal amide bases. Preferably the base is selected from potassium hydroxide, sodium hydroxide potassium t-butoxide or sodium hydride. More preferably the base is potassium t-butoxide or potassium hydroxide.

Suitably the inert diluent is an inert organic solvent commonly used by those skilled in the art which is inert to the base employed. Preferably the diluent is a solvent for compounds II and III. Preferred diluents include hydrocarbons, alcohols, ethers and polar organic solvents and mixtures thereof. More preferred diluents include methanol, ethanol, toluene, dimethyl sulphoxide, N, N-dimethylformamide, and t-butanol or mixtures thereof.

Optionally a phase transfer catalyst as known to those skilled in the art may be used. Preferably the phase transfer catalyst is tetrabutylphosphonium bromide.

Suitably the process is carried out in the temperature range of -10°C to 250°C. Preferably the process is carried out in the range -5°C to 100°C. More preferably the process is carried out in the range 0°C to 50°C. Preferably the reaction is carried out at atmospheric pressure.

Compounds of formula II and III may be prepared by condensing a compound of formula IV



IV

in which R_1, R_2, R_3, R_4 and X are as previously defined

with a compound of formula V

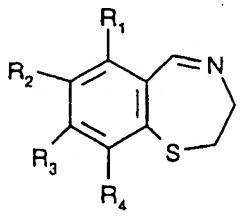
$$H_2N(CH_2)_2SH \qquad V$$

in the presence of an inert diluent. Optionally a salt of V may be employed, for example an acid addition salt.

When an acid addition salt of V is employed, for example the hydrochloride salt, this salt may be first neutralised with a base before reaction with IV. Suitable bases include alkali metal hydroxides, alkali metal hydrides, alkali metal alkoxides, alkali metal carbonates, alkali metal bicarbonates or an amine with a higher basic strength than V.

Preferably the water formed in the reaction is removed by including a dehydrating agent, for example molecular sieves. Alternatively water formed may be removed by azeotropic distillation, for example using toluene.

Compounds of formula I are believed to be novel. In another aspect the present invention provides compounds of formula I



I

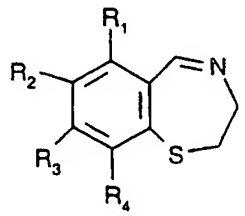
in which

R_1, R_2, R_3 and R_4 independently represent H, halo, alkyl of 1 to 4 carbon atoms or alkoxy of 1 to 4 carbon atoms each alkyl, and alkoxy being optionally substituted with one or more halo.

These compounds are useful intermediates in the preparation of therapeutic agents of formula A. A particularly preferred compound of formula I is 6-chloro-2,3-dihydro-1,4-benzothiazepine.

In a preferred process of the present invention compounds of formula I are prepared directly from compounds of formula IV without isolation of the intermediate II or III.

Thus the present invention also provides a process for the preparation of compounds of formula I

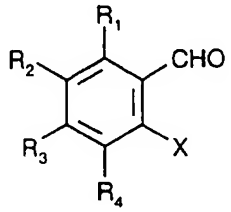


I

in which

R_1, R_2, R_3 and R_4 independently represent H, halo, alkyl of 1 to 4 carbon atoms or alkoxy of 1 to 4 carbon atoms each alkyl, and alkoxy being optionally substituted with one or more halo;

comprising reacting a compound of formula IV



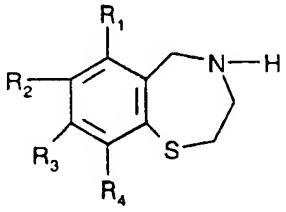
IV

with a compound of formula V

$$H_2N(CH_2)_2SH \qquad V$$

or a salt thereof, in the presence of a base in the presence of an inert diluent.

In a further aspect the present invention provides the use of compounds of formula I in a process to prepare compounds of formula VI

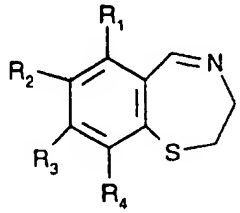


VI

in which

R_1, R_2, R_3 and R_4 independently represent H, halo, alkyl of 1 to 4 carbon atoms or alkoxy of 1 to 4 carbon atoms each alkyl, and alkoxy being optionally substituted with one or more halo;

comprising reacting a compound of formula I



I

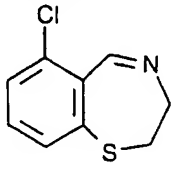
in which R_1, R_2, R_3 and R_4 are as previously defined,

with a reducing agent optionally in the presence of an inert diluent.

Suitable reducing agents include sodium borohydride, lithium aluminium hydride, sodium cyanoborohydride, hydrogen in the presence of a catalyst, sodium and ethanol, sodium amalgam in ethanol, zinc and alkali, zinc and an acid eg. hydrochloric acid, aluminium in alkali eg. sodium hydroxide, aluminium in ethanol,

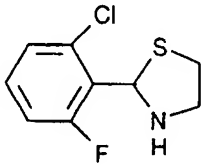
magnesium in methanol, zinc in acetic acid, zinc and water, iron in acid eg. hydrochloric acid, a trialkylammonium formate eg. triethylammonium formate, or by electrolytic means for example in sulphuric acid with a lead or copper cathode. Preferably the reducing agent is sodium borohydride.

In a more preferred process according to the present invention compound VII



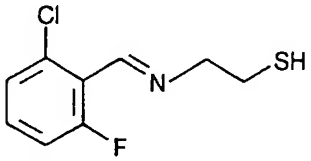
VII

is prepared by reacting compound VIII



VIII

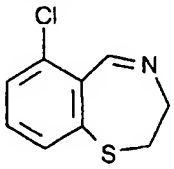
or its tautomer IX



IX

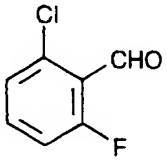
or a mixture of VIII and IX, with a base in the presence of an inert diluent.

In a most preferred process according to the present invention compound VII



VII

is prepared by reacting compound X



X

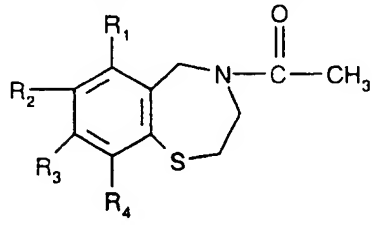
with compound V

$H_2N(CH_2)_2SH$ V

in the presence of a base in the presence of an inert diluent. Optionally a salt of V may be employed for example an acid addition salt.

In a most preferred process according to the present invention compound VII is reacted with a reducing agent in an inert diluent to give 6-chloro-2,3,4,5-tetrahydro-1,4,benzothiazepine. Preferably the reducing agent is sodium borohydride. Preferably the diluent is methanol or a mixture of toluene and methanol.

Compounds of formula VI may be acylated by methods known to those skilled in the art. In yet another aspect the present invention provides the use of compounds of formula VI which have been prepared by the processes of the present invention in the preparation of compounds of formula XI



XI

in which R_1, R_2, R_3 and R_4 are as previously defined.

The process to prepare compounds of formula XI involves reacting compounds of formula VI with acetic anhydride in a solvent, preferably dichloromethane, in the presence of a base, preferably triethylamine. The yields obtained in this process are considerably improved compared to the method described in the prior art (WO 94/11360).

The invention is illustrated by the following non-limitative Examples in which parts and percentages are by weight and compositions of mixed solvents are given by volume. Novel compounds were characterised by elemental analysis and one or more of the following spectroscopic techniques: nuclear magnetic resonance, infra-red and mass spectroscopy.

In the Examples the following abbreviations are used: br = broad; t = triplet; d = doublet; m = multiplet; s = singlet.

Unless otherwise stated, the starting materials used in the Examples are commercially available and may be obtained by reference to the Fine Chemicals Directory.

Example 1

A mixture of 2-chloro-6-fluorobenzaldehyde (2.06 g, 0.013 mol) and 2-mercaptoethylamine (1.00 g, 0.013 mol) in absolute ethanol (20 ml) was boiled under reflux for 4 hours. The mixture was evaporated to dryness under reduced pressure to give 2-(2-chloro-6-fluorophenyl)thiazolidine as an orange oil.

The ^1H nmr ($CDCl_3$) shows a mixture of the thiazolidine and its tautomer in a ratio of 7:1 respectively.

The complex NMR shows δ 2.73 (1H, br.s), 2.9 (~1H, m), 3.1 (~1H, m), 3.25 (~ 1H, m), 3.85 (~1H, m), 5.98 (1H, d) 7.0 (1H, m) 7.2 (2H, m).

The imine tautomer shows diagnostic peaks at 4.0 (CH_2, t) and 8.55 (CH= N, s) at ⅛ intensity (integration) of the thiazolidine peaks.

Example 2

Potassium t-butoxide (1.24 g, 11.05 mmol) was added in one batch to a mixture of 2-(2-chloro-6-fluorophenyl)thiazolidine (2.00 g, 9.2 mmol) in dry dimethyl sulphoxide and (10.0 ml) and dry toluene (10.0 ml) at ambient temperature under nitrogen. An exotherm was observed. After standing for 30 minutes at ambient temperature the mixture was poured into water and extracted with dichloromethane to give an oil which was dissolved in methanol (30.0 ml) and dichloromethane (10.0 ml). Sodium borohydride (500 mg) was added in portions over 10 minutes to the solution. The mixture was evaporated to dryness and water (50 ml) was added to the residue. The mixture was acidified with 5M hydrochloric acid, washed with ethyl acetate, was basified with concentrated sodium hydroxide solution and extracted with dichloromethane to give 6-chloro-2,3-4,5-tetrahydro-1,4-benzothiazepine.

Example 3

a) 2-Mercaptoethylamine hydrochloride (11.36 g, 0.1 mol) was added to a solution of sodium ethoxide in ethanol formed by dissolving sodium (2.30 g) in absolute ethanol (120 ml). A solution of 2-chloro-6-fluorobenzaldehyde (15.85 g,

0.1 mol) in ethanol (50 ml) was added to the mixture and the mixture was boiled under reflux under nitrogen for 3 hours. The mixture was cooled in an ice-water bath, filtered to remove sodium chloride and the filtrate evaporated to dryness under reduced pressure. Toluene was added to the residue and then removed under reduced pressure to remove any water by azeotropic distillation. The mixture obtained was stirred in dichloromethane and filtered. The filtrate was evaporated to dryness to give 2-(2-chloro-6-fluorophenyl)thiazolidine as an oil (21.5 g, 99%).

b) The oil from a) was dissolved in dry N,N-dimethylformamide (50 ml) and added dropwise to a suspension of sodium hydride (4.0 g, of a 60% dispersion in mineral oil) in dry N,N-dimethylformamide (250 ml) at ambient temperature under nitrogen. An exotherm occurred which was controlled by cooling the reaction mixture in a cold-water bath so that the temperature did not exceed 30°C. After the addition the mixture was heated at 55°C for 1 hour. The mixture was cooled to ambient temperature and more sodium hydride (400 mg of a 60% dispersion in mineral oil) was added. The mixture was allowed to stand for 30 minutes and then poured into iced-water (1 l). Solid sodium chloride was added and the mixture was basified to pH 10 with sodium hydroxide and extracted with dichloromethane. The organics were washed with brine and evaporated to give a residue which was partitioned between water (1 l) and ether (500 ml). This resulted in a pale yellow ether solution and a fine buff coloured solid. The aqueous/organic mixture was filtered. The filtrate was separated and the organic layer was dried and evaporated to give a first residue. The buff coloured solid collected by filtration was dissolved in dichloromethane (500 ml) and filtered to remove a beige solid. The filtrate was washed with water, dried and evaporated to give a residue which was combined with the first residue to give 6-chloro-2,3-dihydro-1,4-benzothiazepine as an oily yellow solid (20.26 g).

c) The product from b) (20.26 g) was dissolved in methanol (400 ml) and sodium borohydride (3.8 g, 0.1 mol) added in portions over 1 hour. The mixture was evaporated to dryness under reduced pressure and water (500 ml) was added to the residue. The mixture was acidified with 5M hydrochloric acid to pH 4. The mixture was washed with ethyl acetate (3 x 250 ml) and the aqueous layer was basified with concentrated sodium hydroxide. The basic mixture was extracted with dichloromethane (3 x 400 ml) and the combined extracts were washed with brine,

dried and evaporated to give 6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine. The structure was confirmed by proton nmr in DMSO.

Example 4

Freshly powdered potassium sodium hydroxide (2.12 g, 37.8 mmol) and dried molecular sieves (10.0 g, 4A) were added to a mixture of 2-mercaptoethylamine hydrochloride hydrate (4.98 g, 37.8 mmol) in toluene (50 ml) and dimethyl sulphoxide (50 ml) with stirring under nitrogen. The mixture was stirred for 15 minutes and then 2-chloro-6-fluorobenzaldehyde (5.0 g, 31.5 mmol) was added and the mixture stirred at ambient temperature for 2 hours. Powdered potassium hydroxide (2.82 g, 50.35 mmol) was added and the mixture stirred at ambient temperature for 16 hours. The mixture was poured onto water (1 l) and extracted with ethyl acetate. A beige precipitate which formed was filtered off and washed with ethyl acetate. The organics were combined and the aqueous layer was extracted with ethyl acetate. The combined toluene/ethyl acetate organic layers were washed with water, dried and evaporated to give an oil which was dissolved in ether (500 ml) treated with charcoal, filtered, dried and evaporated to give 6-chloro-2,3-dihydro-1,4-benzothiazepine as an oil. ^{1}H nmr (250 MHz) $CDCl_3$ δ 3.6 (2H,m), 3.76 (2H H,m), 7.15-7.3 (1H,m), 7.3-7.45 (2H,m), 8.6 (1H,s).

Example 5

Sodium borohydride (1.11 g, 29.22 mmol) was added in portions over 20 minutes to a solution of 6-chloro-2,3-dihydro-1,4-benzothiazepine (5.77 g, 29.22 mmol) in IMS (50 ml) and toluene (50 ml). The mixture was evaporated to dryness and water (80 ml) and concentrated hydrochloric acid (20 ml) were added and the mixture heated on a steam-bath for 2 hours and then left at ambient temperature for 18 hours. The acidic solution was washed with ethyl acetate, basified with 5M sodium hydroxide solution and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water, dried and evaporated to give 6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine as a solid, m.p. 57-59°C. ^{1}H nmr $CDCl_3$ 250 (MHz) δ 1.71 (br s,1H), 2.8 (2H, m), 3.35 (2H,m), 4.38 (2H, s), 7.05 (1H,t), 7.25 (1H, dd), 7.45 (1H, dd).

Example 6

a) A mixture of 2-mercaptoethylamine hydrochoride hydrate (100 g, 760 mmol), dried molecular sieves (200 g, 4A), toluene (1000 ml) and dimethyl sulphoxide (1000 ml) was stirred under nitrogen at ambient temperature for 15 minutes. Potassium t-butoxide (86.0 g, 767 mmol) was added and the mixture was stirred for a further 15 minutes at ambient temperature and then 2-chloro-6-fluorobenzaldehyde (100g, 630 mmol) was added. The mixture was stirred at ambient temperature for 2 hours then cooled in an ice-bath and powdered potassium hydroxide (60.0 g, 1071 mmol) was added in 10 gramme portions whilst maintaining the temperature below 10°C. The mixture was allowed to warm up to ambient temperature and stirred at this temperature for 16 hours. The mixture was poured onto water (10 l) and extracted with ethyl acetate to give 6-chloro-2,3-dihydro-1,4-benzothiazepine as an oil which was combined with a repeat preparation on the same scale to give a total of 194 g of product. This oil was dissolved in toluene (500 ml) and methanol (1000 ml) and cooled in an ice-bath. Sodium borohydride (30.0 g, 0.79 mol) was added in portions whilst maintaining the temperature below 10°C. The mixture was allowed to warm to ambient temperature and stirred for a further 2 hours. The solvents were removed under reduced pressure. The residue was partitioned between ether and 5M hydrochloric acid. The acidic layer was heated on a steam-bath for 2 hours and then basified with dilute sodium hydroxide solution and extracted with dichloromethane to give 6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine as an oil (149.2 g).

b) The solid obtained above (149.2 g, 0.747 mol) was dissolved in dichloromethane (800 ml) and triethylamine (250 ml). The mixture was cooled in an ice-bath and acetic anhydride (81.6 g, 0.8 mol) was added dropwise with stirring. The mixture was stirred at approximately 10°C for 2 hours and then washed with dilute hydrochloric acid (1 l) then brine. The organic layer was dried, decolourised with charcoal, filtered and evaporated to give a residue which was triturated with ether to give a solid which was collected by filtration. The solid was identified by nmr spectroscopy as 4-acetyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine, m.p. 83-84°C. Found C, 54.5; H, 4.9; N 5.7; S, 13.3; Cl, 14.4%,$C_{11}H_{12}ClNOS$ requires C, 54.65; H, 5.00; N, 5.8; S, 13.25; Cl, 14.65%.

Example 7

A mixture of 2,6-dichlorobenzaldehyde (3.53 g, 0.02 mol), 2-mercaptoethylamine (1.55 g, 0.02 mol), dried molecular sieves (5.0 g, 4A) and ethanol (50 ml) was boiled under reflux for 3 hours. The mixture was filtered and the filtrate was evaporated under reduced pressure and the residue was dissolved in N,N-dimethylformamide (50 ml). Sodium hydride (1.0 g, of a 60% dispersion in mineral oil, 0.025 mol) was added and the mixture was heated on a steam-bath for 1.5 hours. The mixture was poured onto water (300 ml) and extracted with dichloromethane to give an oil which was dissolved in methanol (50 ml). Sodium borohydride (1.17 g, 0.03 mol) was added to the solution. The solution was allowed to stand for 30 minutes at ambient temperature and then concentrated to around 20 ml and dilute hydrochloric acid added (50 ml, 5M). The mixture was washed with ethyl acetate and the aqueous layer was basified with dilute sodium hydroxide solution and extracted with ether to give 6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine as an oil which solidified on standing and was then recrystallised from cyclohexane to give 2.05 g of product.

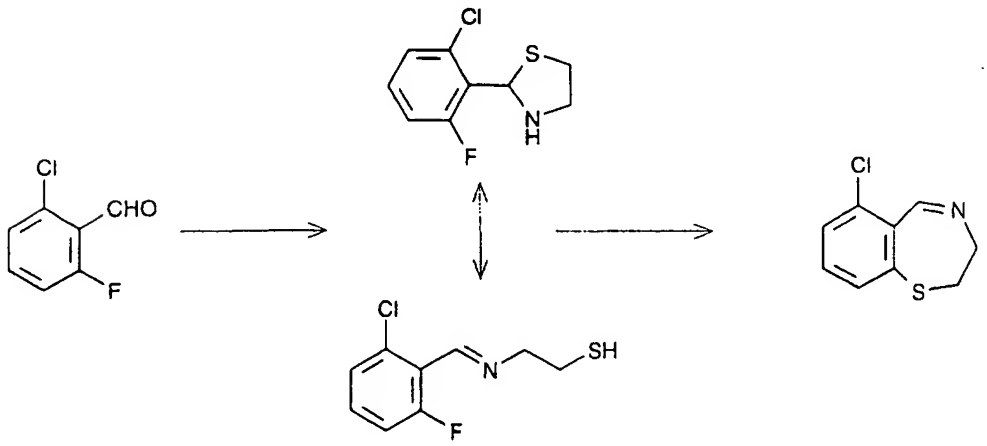
Example 8

6-Chloro-2,3-dihydro-1,4-benzothiazepine (563.3 g) was dissolved in toluene (1.25 l) and then methanol (2.5 l) was added. The solution was cooled to 10°C and sodium borohydride (80 g) was added in portions with stirring over 45 minutes, keeping the temperature between 10 and 20°C. The mixture was stirred at ambient temperature for 2 hours then evaporated to near dryness under reduced pressure to give a residue which was treated with cold water (250 ml). The slurry obtained was poured onto 5M hydrochloric acid (3 l) and the resulting mixture heated on a steam-bath for 2 hours and then left to stand at ambient temperature for 72 hours. The aqueous mixture was washed with ether and then basified with concentrated sodium hydroxide (1.25 l, 12.5M) with cooling. The mixture was cooled to ambient temperature and then dichloromethane (1 l) added. The mixture was stirred for 1 hour and then left to stand for 16 hours. The aqueous layer was separated off and washed with dichloromethane. The combined dichloromethane layer and washings were filtered, dried and evaporated to give 6-chloro-2,3,4,5-tetrahydro-1,4-

benzothiazepine (509.2 g). The solid obtained from the filtration of the dichloromethane was heated on a steam-bath in water (250 ml) then allowed to cool and decanted from an insoluble oily residue, basified with concentrated sodium hydroxide and extracted with dichloromethane to give a further product 28.9 g.

Example 9

a) Preparation of 6-Chloro-2,3-dihydro-1,4-benzothiazepine

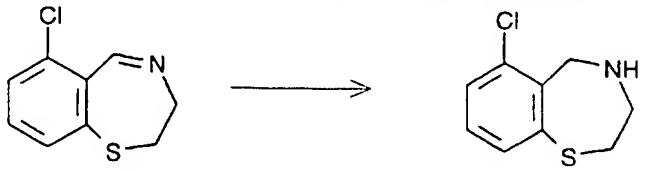


A mixture of dried molecular sieves (4 A, 500g dried in a vacuum oven at approximately 200° for 2 to 4 hours), dimethyl sulphoxide (1.25l), toluene (1.25l) and 2-mercaptoethylamine hydrochloride (250g, approx. 1.90 mol) was stirred at ambient temperature for 15 minutes under a nitrogen atmosphere. The mixture was then cooled in an ice/water bath and potassium t-butoxide (215g, 1.92 mol) was added in portions at <25°) over 5 to 10 minutes. The cooling bath was removed and the mixture stirred for a further 15 min. 2-Chloro-6-fluoro-benzaldehyde (250g, 1.58 mol,) was added and the mixture stirred for a further 2 hours. The mixture was cooled in an ice/water bath to <10° and then treated portionwise with freshly powdered potassium hydroxide (150g , 2.68 mol). The cooling bath was removed and the mixture was stirred overnight. The reaction mixture (excluding the molecular sieves) was poured into water (8l). The molecular sieves were washed with water (2 x 1l) and the washings added to the reaction mixture. The reaction mixture was divided into two equal portions, and each portion was placed in a separating funnel. The molecular sieves were washed with ethyl acetate (2 x 1l). The washings were split into two portions, and a portion was added to each separating funnel. The layers were separated and each aqueous layer was extracted with further ethyl

acetate (3 x 1l). All of the ethyl acetate solutions were combined and concentrated to approx. 1l. The resulting mixture was dissolved in diethyl ether (2.5l) and the resultant solution washed with water (4 x 1l). The ethereal solution was then dried over magnesium sulphate, filtered and evaporated to give 6-chloro-2,3-dihydro-1,4-benzothiazepine as a brown oil.

^{1}H nmr (250 MHz) $CDCl_3$ δ 3.60-3.55 (2H, m); 3.80-3.75 (2H, m); 7.30-7.15 (1H, m); 7.40-7.35 (2H, m); 8.60 (1H, s).

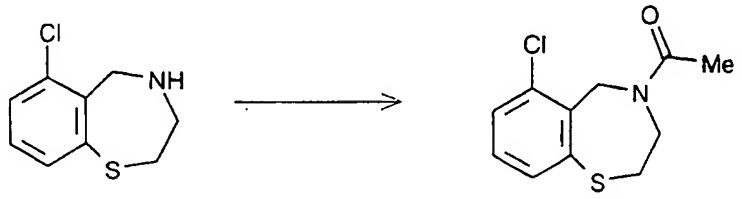
b) Preparation of 6-Chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine



The imine (approx 2.57 mol,) was dissolved in toluene (1.2l,). The stirred reaction mixture was diluted with methanol (2.4l). The reaction mixture was cooled in an ice/water bath to <10° and then sodium borohydride (78.5g, 2.07 mol) was added in portions at <10° over 1 hour. The cooling bath was removed and the mixture was stirred for a further 2 hours. The reaction mixture was concentrated to approximately 1l on a rotary evaporator. The mixture was then added cautiously to vigorously stirred hydrochloric acid (2.5l, 5M) in 5l beaker in an ice/water bath The mixture was diluted with diethyl ether (2l) and stirred vigorously for 15 minutes. The layers were separated [Note 1: if a solid precipitate had formed the following procedure was followed : The mixture was filtered and the solid was washed with diethyl ether and then sucked dry overnight. The aqueous/ethereal filtrate was separated. The aqueous layer was washed with diethyl ether and then recombined with the solid] and the aqueous layer washed with further diethyl ether (1l). The aqueous solution (or aqueous suspension if the procedure of Note 1 was used) was placed in a 10l split-neck flask equipped with an overhead stirrer. The mixture was stirred vigorously and heated on a steam bath for 2 hours. The mixture was stirred and cooled in an ice/water bath and then basified with aqueous sodium hydroxide solution (12.5M) to >pH 10 to give an oil. Dichloromethane (2l) was added and the mixture stirred for 15 minutes. The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 500ml). The dichloromethane solutions were combined, dried over magnesium sulphate and then filtered. Charcoal was

added to the filtrate which was stirred for 15 min, filtered and evaporated on a rotary evaporator to give the desired product as an oil which solidified on standing. The product was analysed by glc (12QC5RTX20 column) and ^{1}H-nmr spectroscopy ($CDCl_3$). For 11 runs of this reaction the corrected overall yield was 89%, with yields ranging from 83% to 92%.

c) Preparation of 4-acetyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine



The amine (approx. 2.35 mol) was dissolved in dichloromethane (2.4l). The stirred mixture was diluted with triethylamine (432ml, 3.11 mol,) to give a clear solution and then cooled in an ice/water bath. Acetic anhydride (254ml, 2.70 mol) was added dropwise at <10° over 30 minutes and the resulting solution was then stirred in the ice/water bath for 2 hours. Hydrochloric acid (2M, 2l) was added to the stirred mixture in an ice/water bath. The mixture was then stirred for a further 5 min, the mixture transferred to a separating funnel and the layers separated. The dichloromethane solution was washed with hydrochloric acid (2M, 1.5l) followed by saturated brine. The dichloromethane solution was then dried over magnesium sulphate, filtered, stirred with charcoal, filtered and evaporated on a rotary evaporator to give an oil. This oil was then treated with diethyl ether (2.5l) and the mixture left to stand overnight. The mixture had become a clear solution over an oil/crystal mixture. The solution was carefully decanted from the oil/crystal mixture and then cooled and scratched in an ice/water bath. [Note 2 The oil/crystal mixture was rich in the desired product. If a significant quantity of this oil was obtained the desired product could be isolated as described below:- The oil/crystal mixture was dissolved in dichloromethane (400ml) and evaporated on a rotary evaporator to give an oil. This oil was dissolved in boiling ethyl acetate (350ml), hot filtered and cooled. The resultant crystalline solid was collected by filtration, washed with ice-cold ethyl acetate (2x50ml) and dried to give the desired product. The resultant precipitate was collected by filtration, washed with diethyl ether (2x400ml) and dried to constant weight in a vacuum oven at 60-65° to give the desired product. Further crops of product were obtained by concentrating the combined ethereal filtrate and washings to small volume and cooling the resultant solution.

In 10 runs of this reaction, the overall conversion of amine (3684g corrected weight) to product (2243g) was 50%, with yields ranging from 37% to 65% but generally in the range 44-55%.

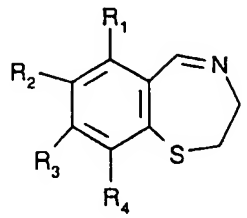
Comparative Example

The preparation of 6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine from 2-chloro-6-nitrobenzonitrile known in the art gave an overall yield of 19.25%.

The preparation of 6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine from 2-chloro-6-fluorobenzaldehyde according to the present invention gave an overall yield of 59.25%.

Claims

1. A process for the preparation of compounds of formula I

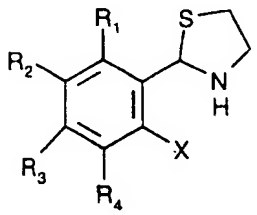


I

in which

R_1, R_2, R_3 and R_4 independently represent H, halo, alkyl of 1 to 4 carbon atoms or alkoxy of 1 to 4 carbon atoms each alkyl and alkoxy being optionally substituted with one or more halo;

comprising ring opening and re-cyclising a compound of formula II



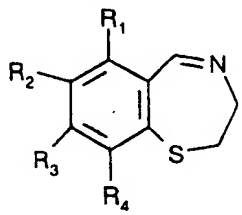
II

in which

R_1, R_2, R_3 and R_4 are as previously defined and X is a group which is susceptible to nucleophilic displacement by sulphur;

in the presence of a base in the presence of an inert diluent.

2. A process for the preparation of compounds of formula I

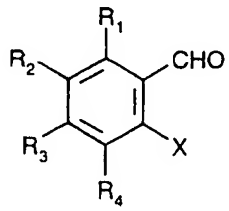


I

in which

R_1, R_2, R_3 and R_4 independently represent H, halo, alkyl of 1 to 4 carbon atoms or alkoxy of 1 to 4 carbon atoms each alkyl, and alkoxy being optionally substituted with one or more halo;

comprising reacting a compound of formula IV



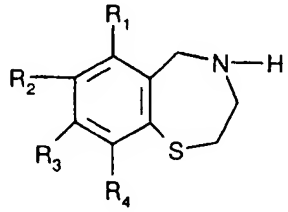
IV

with a compound of formula V

$$H_2N(CH_2)_2SH \qquad V$$

or a salt thereof, in the presence of a base in the presence of an inert diluent.

3. A process to prepare compounds of formula VI

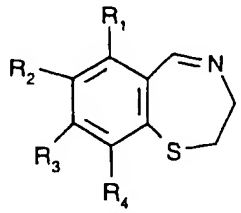


VI

in which

R_1, R_2, R_3 and R_4 independently represent H, halo, alkyl of 1 to 4 carbon atoms or alkoxy of 1 to 4 carbon atoms each alkyl, and alkoxy being optionally substituted with one or more halo;

comprising reacting a compound of formula I



I

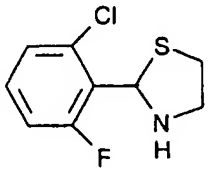
in which R_1, R_2, R_3 and R_4 are as previously defined,

with a reducing agent optionally in the presence of an inert diluent.

4. A process to prepare compound VII

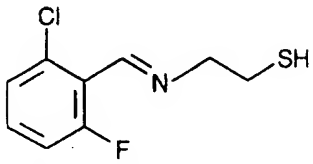
VII

comprising reacting compound VIII



VIII

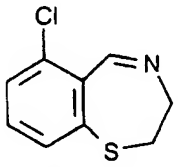
or its tautomer IX



IX

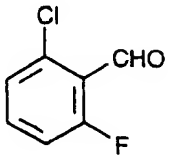
or a mixture of VIII and IX, with a base in the presence of an inert diluent.

5. A process to prepare compound VII



VII

comprising reacting compound X



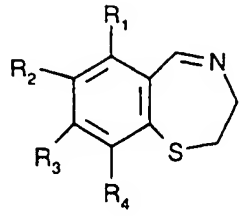
X

with compound V

$H_2N(CH_2)_2SH$ V

in the presence of a base in the presence of an inert diluent.

6. Compounds of formula I

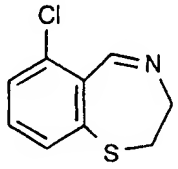


I

in which

R_1, R_2, R_3 and R_4 independently represent H, halo, alkyl of 1 to 4 carbon atoms or alkoxy of 1 to 4 carbon atoms each alkyl, and alkoxy being optionally substituted with one or more halo.

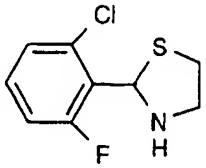
7. The compound of formula VII



VII

which is 6-chloro-2,3-dihydro-1,4-benzothiazepine.

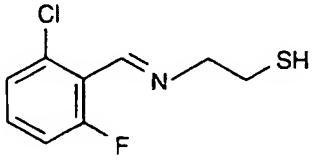
8. The compound of formula VIII



VIII

which is 2-(2-chloro-6-fluorophenyl)thiazolidine.

9. The compound of formula IX



IX

which is N-(2-chloro-6-fluorobenzylidene)-2-mercaptoethylamine.

10. A process as claimed in claim 3 in which the reducing agent is sodium borohydride.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/03945

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D281/10 C07D277/04 C07C323/25

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 107, no. 12, 1987 Columbus, Ohio, US; abstract no. 108127p, J.W.L. MARTIN ET AL.: "Copper(I) complexes of 14- and 16-membered chelating macrocycles with trans-disposed pairs of imine-N and thioether-S donors: crystal and molecular structures of [Cu(C18H18N2S2)]CF3SO3 and [Cu(C20H22N2S2)]CF3SO3" page 775; XP002044897 see abstract & INORG. CHEM., vol. 26, no. 18, 1987, pages 2963-8, --- -/--	3,6,10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

2

Date of the actual completion of the international search	Date of mailing of the international search report
29 October 1997	07. 11. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allard, M

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INTERNATIONAL SEARCH REPORT

Inte. .ional Application No
PCT/EP 97/03945

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	D. BESANTY ET AL.: "Synthèse de benzo et dibenzothiazépines nitrées à visée anti-parasitaire" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 23, no. 4, 1988, PARIS, FR, pages 403-5, XP002044895 cited in the application see the whole document, particularly page 403, scheme 2	1,2,4,5, 8,9
Y	WO 94 11360 A (THE BOOTS COMPANY PLC) 26 May 1994 cited in the application see the whole document	1-10
Y	WO 93 16055 A (THE WELLCOME FOUNDATION LIMITED) 19 August 1993 see the whole document, particularly page 12, first paragraph	1-10
Y	A. GAROFALO ET AL.: "Benzothiazine and benzothiazepine derivatives: synthesis and preliminary biological evaluation" IL FARMACO, vol. 48, no. 2, 1993, PAVIA, IT, pages 275-83, XP002044896 see the whole document, particularly page 279, scheme 5, and page 280, lines 4-8	1,2,4,5, 8,9
Y	WAI-KAH GOH ET AL.: "Molybdenum(VI) complexes of Schiff bases derived from salicyladehyde and 2-aminoethanol (cysteamine)" AUSTRALIAN JOURNAL OF CHEMISTRY, vol. 37, no. 11, 1984, MELBOURNE, AU, pages 2235-42, XP002044947 see the whole document, particularly page 2239, scheme 1	1,4,8,9

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter.. ..onal Application No
PCT/EP 97/03945

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9411360 A	26-05-94	AU 680639 B	07-08-97
		AU 5464494 A	08-06-94
		BG 99679 A	30-04-96
		CA 2148584 A	26-05-94
		CZ 9501176 A	12-06-96
		EP 0667866 A	23-08-95
		FI 952204 A	08-05-95
		HU 71819 A	28-02-96
		JP 8503202 T	09-04-96
		NO 951797 A	24-05-95
		NZ 257843 A	28-10-96
		PL 308757 A	21-08-95
		SK 58895 A	13-09-95
		US 5580866 A	03-12-96
WO 9316055 A	19-08-93	AU 675419 B	06-02-97
		AU 3508293 A	03-09-93
		CA 2117485 A	19-08-93
		EP 0626952 A	07-12-94
		FI 943775 A	16-08-94
		HU 71487 A	28-11-95
		IL 104740 A	12-09-96
		JP 7503724 T	20-04-95
		MX 9300821 A	01-09-93
		NZ 249189 A	27-02-96
		US 5663165 A	02-09-97
		ZA 9301073 A	16-08-94